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Mechanisms in manganese catalysed oxidation of alkenes with H_2O_2

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The development of new catalytic systems for *cis*-dihydroxylation and epoxidation of alkenes, based on atom economic and environmentally friendly concepts, is a major contemporary challenge. In recent years, several systems based on manganese catalysts using H_2O_2 as the terminal oxidant have been developed. In this review, selected homogeneous manganese catalytic systems, including 'ligand free' and pyridyl amine ligand based systems, that have been applied to alkene oxidation will be discussed with a strong focus on the mechanistic studies that have been carried out.

Introduction

A central challenge in modern chemical synthesis is to replace economically and environmentally unsustainable and energy demanding methods. The continued reliance of contemporary synthetic methods on predominantly stoichiometric atom inefficient oxidants, such as peracids, chromates, permanganates and OsO_4, reflects in large part the challenge that is faced. In addition to the evident environmental benefits, catalyst development is also driven by the increased scarcity of metals such as ruthenium and osmium. Indeed, it is this latter aspect that places 1st row transition metal catalysed oxidation[1] with O_2 and H_2O_2 at centre stage,[2–4] in particular systems based on titanium,[5] copper,[6] iron and manganese.[7–10]

Manganese, together with iron,[11,12] has proven to be one of the more promising metals on which to base new catalytic oxidation systems. In the case of manganese, this is in large part due to the remarkably versatile redox chemistry of manganese with the formal oxidation states II–V and VII being readily accessible. Initial interest regarding manganese coordination

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Pattama Saisaha

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Johannes W. de Boer

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chemistry focussed on developing structural and functional mimics for manganese catalases and the oxygen evolving complex of photosystem II.[13,14] However, over the last two decades the focus has shifted towards applying such complexes as oxidation catalysts.

In this review a select group of manganese based homogeneous catalyst systems for alkene oxidation will be discussed. These systems have received attention with regard to the mechanism by which the catalysts work and their potential active intermediates. Manganese porphyrin, Schiff base and, especially, the salen ligand[15–17] based systems have been discussed elsewhere in depth and hence will not be discussed here; the interested reader is directed to reviews on these latter systems.[7,18] In addition, the substrate scope of individual systems will be discussed only where relevant with regard to mechanistic considerations. Finally, because of the increased importance placed on sustainability in chemical processes, this review will be limited to systems that employ H_2O_2 to effect alkene oxidation and, in some cases for comparison, using peracetic acid as terminal oxidant.

The goal of this review is to survey the various approaches that have been taken to understand how these catalysts actually work and, in particular, to understand the role of additives in controlling reactivity.

Studying mechanisms in manganese catalysed oxidation chemistry: tools of the trade[19]

One of the major challenges in studying manganese based catalytic systems is that Mn^{II} ions and complexes are essentially spectroscopically white (high spin d^5) and highly labile, making detection difficult, except for mononuclear Mn^{II} complexes, often even by EPR spectroscopy and mass spectrometry. In the case of EPR spectroscopy[20] the range of oxidation and spin states that can be obtained with manganese is unusually broad and hence this technique is one of the few available to probe metal oxidation states and environments *in situ.*

Mononuclear high spin Mn^{II} complexes are characterised by a strong 6-line ($s = 5/2$) signal at *ca.* $g = 2$. For di- and multinuclear complexes the EPR spectra are generally more informative, but signals may be weaker than those for mononuclear Mn^{II}, and can be quite complex in terms of g values and hyperfine coupling.

Mn^{III} and Mn^{IV} mono- and multi-nuclear complexes are kinetically much more stable with regard to ligand exchange and exhibit, generally, quite intense UV absorption bands, assigned to ligand to metal charge transfer transitions, and moderately intense visible and near-infrared absorption bands, the latter bands generally being assigned to metal centred transitions. Mononuclear (HS) Mn^{III} and Mn^{IV} complexes show 6-line EPR spectra typically at $g = 2$, and 4, respectively; however they are often difficult to observe due to line broadening and are dependent on the crystal field strength of the complex.

Both $Mn^{IV,IV}{}_2$ and $Mn^{III,III}{}_2$ dinuclear complexes are EPR silent in general; however their diamagnetic and paramagnetic (*i.e.* over a 100 to −100 ppm range) ^1H NMR spectra can be informative and in some cases detailed assignments have made use of deuterium isotope labelling.[21] By contrast, the mixed valent $Mn^{II,III}{}_2$ and $Mn^{III,IV}{}_2$ complexes show quite rich EPR spectra that are characteristic of each redox state. For example $Mn^{III,IV}{}_2$ dimers exhibit a characteristic 16-line spectrum at *ca.* $g = 2$.

Conveniently the complexes in oxidation states higher than Mn^{II} are typically sufficiently stable towards ligand exchange to allow for mass spectral studies to be of use, albeit even for these systems, care should be taken in assignments made, as ligand and indeed changes in redox state can occur under the conditions of electrospray measurements.[22]

With regard to mechanistic studies, however, perhaps two of the most powerful tools in manganese oxidation catalysis,[23] and indeed in most areas of catalysis, are kinetics and isotopic labelling both for kinetic isotope effect determination and, more importantly, for atom tracking of oxygen. Identification of the origin of the oxygen atoms(s) incorporated into products is important as, in addition to the oxidant H_2O_2, oxygen (O_2), solvent and/or H_2O can be a source of the oxygen atoms.

A key challenge with regard to kinetics is that sufficient data are necessary in order to achieve reliable fits. Furthermore, in general, kinetic studies only provide information up to and including the rate determining step in a reaction. This latter point can be overlooked easily and is made more challenging by the fact that in many systems the rate determining step and indeed the mechanism itself can change as conditions are varied.

Finally, the role of computational chemistry in mechanistic research continues to increase, despite the challenge presented by manganese systems, especially Mn^{II}, and has already made important contributions to the field (*vide infra*).

Wesley R. Browne

*Wesley R. Browne received his BSc in Pure and Applied Chemistry and PhD in Chemistry (*2002*) from Dublin City University (DCU), Dublin, Ireland, under Prof. J. G. Vos and was awarded the Young Chemists Award from the Royal Irish Academy for his doctoral dissertation. His doctoral research focused on ruthenium polypyridyl photochemistry and photophysics. After Post-Doctoral positions at Queens University Belfast, under Prof. J. J. McGarvey and subsequently at the University of Groningen under Prof. B. L. Feringa, he was appointed as assistant Professor at the Stratingh Institute for Chemistry in* 2008*. In* 2007*, he was awarded a VIDI Innovational research award from The Netherlands Organisation for Science (NWO) and, in* 2011*, an ERC Starting Investigator Grant by the European Research Council. His research interests include electrochemistry and Raman spectroscopy and microscopy applied in particular to oxidation catalysis and molecular based materials.*

Oxidations catalysed by 'ligand free' Mn systems

Perhaps the simplest manganese based catalyst system, at least from the point of view of catalyst composition, is to use Mn^{II} salts with H_2O_2 in aqueous solvents. Indeed the oxidation of alkenes with Mn^{II} salts and H_2O_2 in carbonate buffer had been noted by Hage and co-workers in the 1990s,[24] and Richardson *et al.* have reported that the epoxidation of alkenes could be achieved with $NaHCO_3/H_2O_2$ alone (*i.e.* without deliberate addition of metal ions).[25]

Burgess and co-workers placed the use of Mn^{II} salts as catalysts on a synthetically applicable level in what is a remarkably simple and effective 'ligand free' Mn-based epoxidation system.[26,27] Under their typical conditions, using 0.1–1.0 mol% $MnSO_4$ and 30% aqueous H_2O_2 (10 equiv. with respect to the substrate) as oxidant, (Fig. 1), in bicarbonate buffer a substantial increase in both the yield and the rate of reaction was achieved, compared with the metal free system reported by Richardson *et al.*[25]

With regard to scope, limited solubility of substrates demanded the use of organic co-solvents such as ^{t}BuOH or DMF. The system allowed for conversion of cyclic, aryl- and trialkyl-substituted alkenes to their corresponding epoxides in high yields; however, terminal alkenes were unreactive.[26] Although the system is 'ligand free', Burgess and co-workers explored the use of additives to enhance activity towards epoxidation and, importantly, to suppress wasteful decomposition of H_2O_2.[27] This latter issue has driven the use of additives in other manganese based catalytic systems as will be discussed below. The optimum conditions for epoxidation with respect to yield, decreased reaction times and H_2O_2 consumption (2.8–5 equiv.) were found to be sodium acetate (6 mol%) in ^{t}BuOH or salicylic acid (4 mol%) in DMF.

From a mechanistic perspective a key feature of the system is the necessity for bicarbonate to be present (*i.e.* as buffer). In addition to acting as a buffer, it has been shown by ^{13}C NMR spectroscopy that a peroxymonocarbonate ion (HCO_4^-) forms *in situ* (Fig. 2). Upon mixing of $NaH^{13}CO_3$ (at δ 160.4 ppm) with H_2O_2 in ^{t}BuOH, a ^{13}C signal appeared at δ 158.5 ppm that corresponds to the chemical shift of peroxymonocarbonate.[27] Saturation transfer NMR spectroscopy indicated that the equilibrium between peroxymonocarbonate and bicarbonate is established rapidly.[26] EPR spectroscopy of the reaction mixture before the reaction showed the characteristic 6-line spectrum of mononuclear Mn^{II}, centred at *ca.* $g = 2$. The signal decreased in intensity upon addition of H_2O_2 and disappeared completely within several minutes. The 6-line signal was replaced by a broad signal at $g = 4$, characteristic of high-spin mononuclear Mn^{IV}. As the reaction reached completion the 6-line signal of mononuclear Mn^{II} recovered. These data suggest that the resting state for the manganese ion under reaction conditions is a Mn^{IV} species rather than a Mn^{II} species. When the H_2O_2 concentration decreases to a certain level, reoxidation of the Mn^{II} ions becomes the rate limiting step in the catalytic cycle. The authors[27] surmised that the Mn^{II} ions activate HCO_4^- by acting as a Lewis acid (Scheme 1). The EPR data and the fact that most other metal salts screened were unreactive, despite the fact that many of them have comparable Lewis acidities to $MnSO_4$, suggest that the actual mechanism is more complicated.

Another pathway proposed involved a manganese η^2-peroxymonocarbonate ($[Mn^{II}\text{-}\eta^2\text{-}HCO_4]^+$) (**A**) species (Scheme 2). This species can be generated either from peroxymonocarbonate

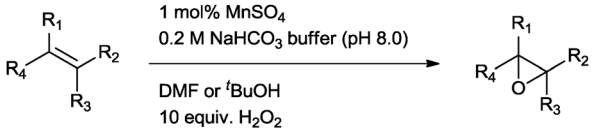


Fig. 1 Typical reaction conditions employed by Burgess and co-workers for the manganese catalysed epoxidation of alkenes with bicarbonate/hydrogen peroxide.[26]

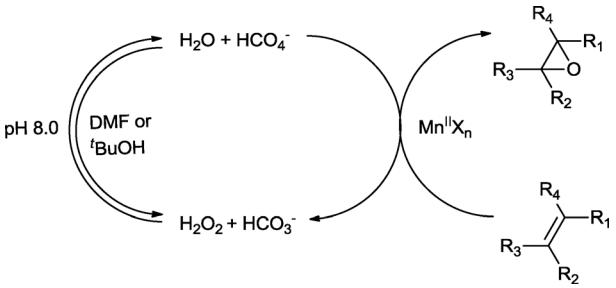
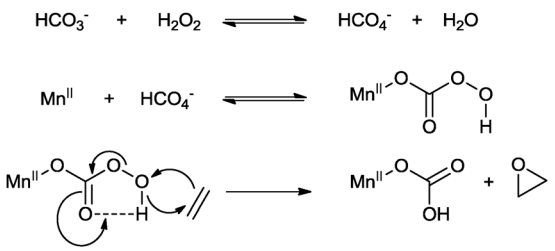
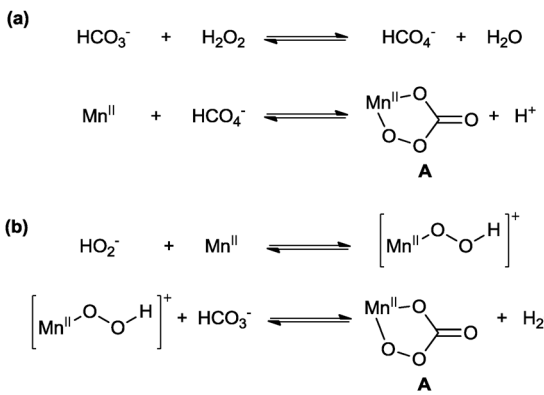


Fig. 2 Proposed catalytic cycle for manganese catalysed epoxidation with bicarbonate/hydrogen peroxide, where X_n is an undefined ligand.[26,27]



Scheme 1 Epoxidation mechanism relying on Mn^{II} acting as a Lewis acid.[27]



Scheme 2 Formation of peroxymonocarbonate complex **A** (a) by direct reaction of peroxymonocarbonate and (b) by reaction of peroxy complex with bicarbonate.

(HCO_4^-) coordinated directly with Mn^{II} or HO_2^- coordination to Mn^{II} followed by coordination of bicarbonate (Scheme 2). Pathway **b** would be facilitated by an increase in pH and *vice versa*. The decreased levels of epoxidation observed at higher pH and the relatively high pK_a of H_2O_2 suggests that it is the peroxymonocarbonate that coordinates to the manganese (pathway **a** in Scheme 2).

With regard to oxygen transfer to the alkene, it remains unclear whether intermediate **A** epoxidises the alkene directly or *via* a Mn^{IV}=O species. Of particular note is the observed lack of stereoretention in the oxidation of *cis*- and *trans*-acyclic disubstituted alkenes, which indicates a stepwise oxygen atom transfer process. Overall, however, at present there is insufficient evidence for involvement of either the peroxy species or the Mn^{IV}=O species in oxygen transfer to the alkene.

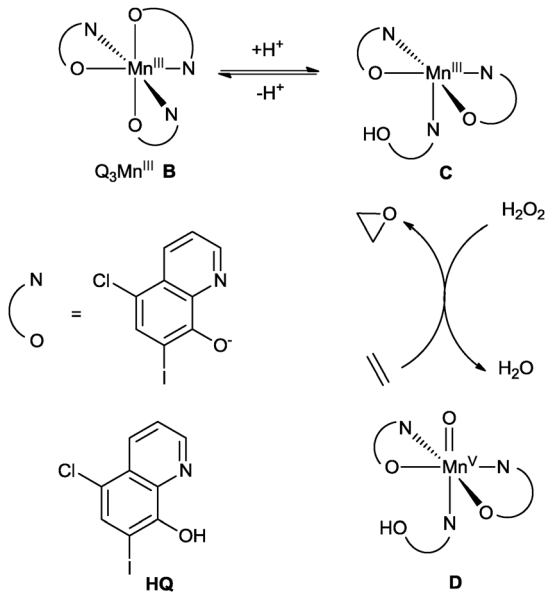
Although, not based on a simple manganese salt, the system reported by Kwong *et al.*[28] demonstrated the activity of a relatively simple Mn^V complex, $[Mn^V(N)(CN)_4]$, originally reported by Wieghardt and co-workers.[29] The system shows remarkable efficiency in the epoxidation of alkenes with, as for the system of Burgess and workers above, lower reactivity being observed for terminal alkenes. Oxidation of primary and secondary alcohols was also found to be efficient. Of importance with regard to mechanism is the retention of configuration observed for *cis*-stilbene, which suggests an essentially concerted oxygen transfer process. Furthermore, the mechanistic probe 2-methyl-1-phenyl-2-propyl hydroperoxide indicated that heterolysis of the O–O bond occurs rather than homolysis.[30]

The effect of additives, a recurring theme in manganese catalysed oxidation with H_2O_2, was also studied.[28] Acetic acid was found to have a moderate positive effect on yields and a considerable effect on reaction rates. One could argue that this may indicate the formation of peracetic acid *in situ*, however, as noted in other studies (*vide infra*), this can be discounted under the conditions employed.

Instead, DFT calculations indicate that the manganese centre acts as a Lewis acid to activate the O–O bond of H_2O_2 towards heterolytic cleavage rather than the formation of a high valent manganese-oxo species.[28] In addition, on the basis of calculated intermediates, it is proposed that the role of acetic acid is to weaken the O–O bond further through hydrogen bonding interactions and to facilitate proton transfer.

Pyridyl and quinoline based ligands for manganese catalysed oxidation

It is arguable whether or not it is appropriate to use the label 'ligand free' in catalyst systems based on manganese salts, since, in principle, when additives are used to promote activity, these additives can potentially form defined complexes. In the case of pyridine based additives, it is generally assumed that they promote activity by acting as ligands, with the catalysts being formed *in situ.* Perhaps one of the most simple pyridine based ligands applied to manganese based oxidation catalysis with H_2O_2 are the 8-hydroxyquinolines.

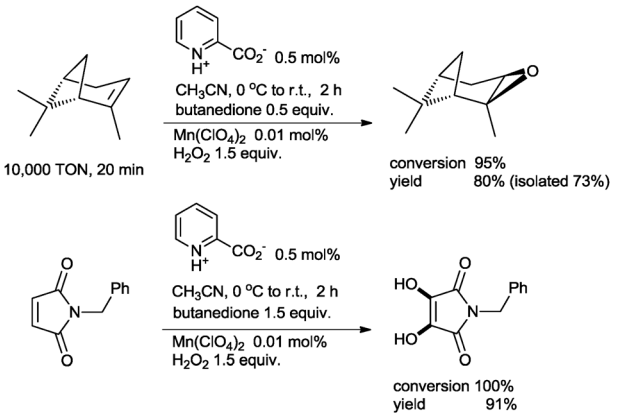


Scheme 3 Proposed mechanism for epoxidation of alkenes using Mn–quinoline complex and H_2O_2.[31]

Zhong and co-workers reported a manganese catalyst based on 6-chloro-8-hydroxy-7-iodo-quinoline (**HQ**, Scheme 3).[31] The authors demonstrated that the system is highly efficient in the epoxidation of a broad range of alkenes with H_2O_2 in acetone/water. The catalyst can be prepared *in situ* by mixing the ligands with Mn^{II} salts or, alternatively, the tris-complex Q_3Mn^{III} (Scheme 3) can be prepared in advance.

The coordination mode of the complex was found to be pH dependent and the activity can be 'switched' on and off by changes in pH. Notably, the preformed complex (Q_3Mn^{III}) gave low substrate conversion. As with the system of Burgess and co-workers described above,[26,27] weakly acidic additives, *e.g.*, NH_4Cl or NH_4OAc–AcOH, increased conversion, whereas basic additives, except $NaHCO_3$, resulted in a decrease in conversion. In the case of addition of $NaHCO_3$, the increased activity is possibly due to formation of the peroxymonocarbonate ion (HCO_4^-) as noted by Burgess and co-workers.[26] This latter point highlights a common difficulty in the field in which tuning of reaction conditions can sometimes lead to convergence of conditions between systems that are, at first sight, quite different.

Notwithstanding this, the **HQ** based system of Zhong *et al.*[31] allows for epoxidation of both aliphatic and aromatic alkenes where acid-sensitive epoxides are formed. This latter observation suggests that the ligand decreases the Lewis acidity of the Mn^{III} ion and hence the propensity for the catalyst to engage in catalytic epoxide ring opening. Although the spectroscopic data available are limited, the authors proposed that a pendant R–OH group in species **C** (Scheme 3) is important in the reaction and plays two roles; firstly, it acts as a labile ligand that inhibits the formation of potentially inactive μ-oxo-manganese dimers and, secondly, it facilitates O–O bond cleavage through hydrogen bonding interactions. This mechanism rationalises the low



Scheme 4 Conversions and (isolated) yields obtained for the epoxidation of selected alkenes using the Mn^{II}–pyridine-2-carboxylic acid–butanedione system. Substrates were 0.5 M.[34]

substrate conversion observed in the presence of basic additives, such as imidazole, which would shift the equilibrium in favour of species **B**.

Saisaha *et al.*[32] reported an *in situ* formed catalyst system for the oxidation of alkenes with H_2O_2 based on pyridine-2-carboxylic acid, a manganese salt, a base (*e.g.*, NaOH or NaOAc) and a ketone, discovered during a mechanistic study of polypyridylamine based manganese catalysts (*vide infra*).[33] The system is highly effective in the epoxidation of electron-rich alkenes and the *cis*-dihydroxylation of electron-poor alkenes (Scheme 4).[34]

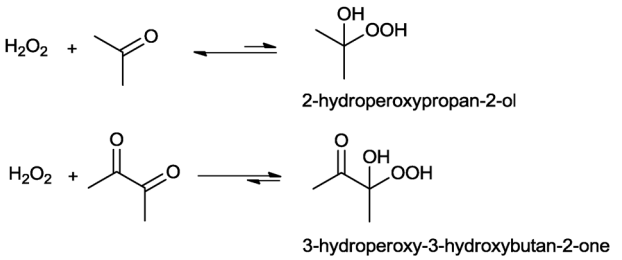
The system is highly active and can achieve up to 300 000 turnovers with respect to Mn^{II} with turnover frequencies of up to 40 s^{-1} with 1.5 equiv. of H_2O_2 with 0.001 mol% $Mn(ClO_4)_2$.[34] However, the high activity, low catalyst loadings needed (0.01–0.3 mol%) and the absence of spectroscopic signals assignable to manganese species (*e.g.*, by EPR or UV/Vis spectroscopy) means that direct identification of an 'active species' or even the catalyst in its resting state was essentially impossible. Nevertheless, mechanistic insight into the reaction with regard to other reaction components was obtained.

The system relies on the presence of a ketone in order to function, either as solvent or (sub)stoichiometrically, and mechanistic studies on this system have revealed that the ketone reacts with H_2O_2 to form the active oxidant in the reaction (Scheme 5).

UV/Vis absorption and Raman spectroscopy allowed for identification of the role of the ketone in the reaction. Addition of a slight excess of H_2O_2 (1.5 equiv.) to the reaction mixture containing butanedione results in immediate and quantitative conversion of the butanedione to 3-hydroperoxy-3-hydroxy-butan-2-one. This latter species reacts with the catalyst to form the active oxidant species.

UV/Vis absorption spectroscopy shows that the characteristic n–π* absorption of the butanedione was almost completely lost within several seconds of addition of H_2O_2 (Fig. 3). The absorption recovers after several minutes once the H_2O_2 concentration decreases below that of the butanedione. Importantly, although the butanedione is consumed partly in the reaction, it is nevertheless catalytic with respect to the oxidation of the alkene substrates. The fate of the butanedione was also investigated. Decomposition of butanedione to acetic acid was determined by ^{13}C NMR spectroscopy and shown to be a side reaction, albeit an important one.[34] Again, the potential involvement of peracetic acid was considered; however, in this case it was confirmed that peracetic acid is not formed from H_2O_2 and acetic acid under the reaction conditions employed.[34]

A mechanistically important observation is the lack of retention of configuration in the epoxidation of *cis*-/*trans*-2-heptene and several other alkenes, which contrasts with the complete retention of configuration for the (minor) *cis*-diol product (Scheme 6).



Scheme 5 Reaction between ketones and H_2O_2. In the case of butanedione the equilibrium lies predominantly to the right.[34]

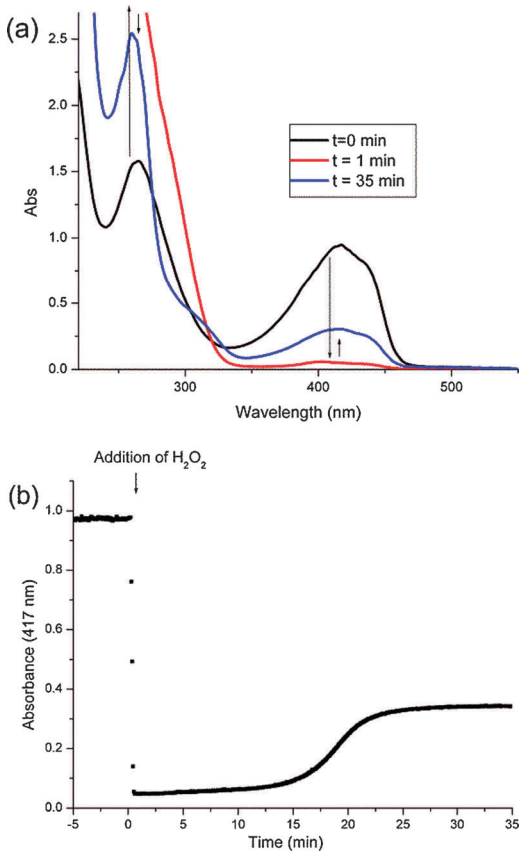
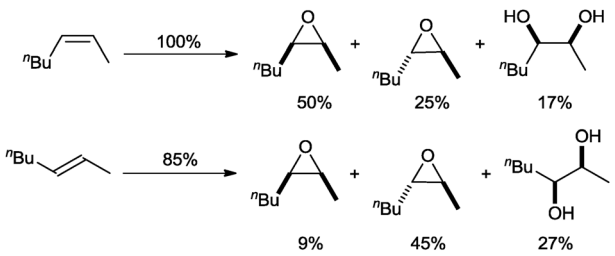


Fig. 3 (a) Changes in the UV/Vis absorption spectrum of the reaction mixture 1 min and 35 min after addition of H_2O_2. (b) Absorbance of the butanedione at 417 nm over time. Reproduced with permission from ref. 34. Copyright ACS 2012.



Scheme 6 Oxidation of *cis*-/*trans*-2-heptene. For conditions see Scheme 4.[34]

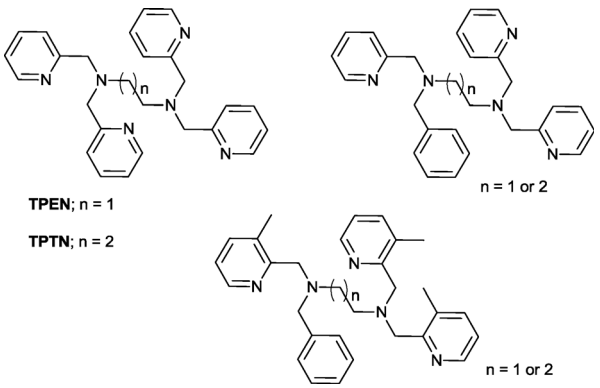


Fig. 4 Structure of TPEN/TPTN ligands and their derivatives.[37,38]

Together with the absence of allylic oxidation of cyclohexene, it can be envisaged that although hydroxyl (or similar) radicals are not generated in the reaction, the epoxidation is stepwise.

From the point of view of application, simplicity in catalyst composition, *i.e.* the use of off-the-shelf components, is highly desirable. However, such simplicity in terms of catalyst composition does not necessarily mean that the mechanisms by which such systems operate are equally straightforward. For the system described above the very low catalyst concentrations (as low as 500 nM in the case of Mn^{II}–pyridine-2-carboxylic acid)[34] pose a massive challenge in mechanistic studies. Nevertheless these studies are highly valuable in understanding how individual components are involved in the reaction and, more importantly, why components affect reactions in a negative or positive manner. Such insights pave the way towards more generally applicable systems.

Polypyridyl amine based ligands for manganese catalysed oxidations

While the development of 'ligand free' catalyst systems is highly desirable in terms of alkene epoxidation and *cis*-dihydroxylation where stereochemistry is not a consideration, the paradigm for achieving stereocontrol over oxidation reactions is to employ well defined complexes in which the chiral environment is provided by a ligand. This paradigm has driven the design and synthesis of ligands for manganese based catalysts over recent decades, with the ultimate goal of achieving the same level of control achieved with, *e.g.*, osmium based catalysts.[35] Perhaps the most successful ligand systems, to date, are those based on porphyrins[18] and salens[15] using oxidants such as oxone and NaClO. However, with notable exceptions, enantioselectivities and, especially, turnover numbers are limited when H_2O_2 is used as the terminal oxidant.[36]

A key challenge faced by the field has been to design ligand systems that can be tuned easily and are based on readily available chiral reagents, such as 1,2-diaminocyclohexane.

Dinuclear manganese complexes based on the TPTN/TPEN ligands (Fig. 4) (where TPTN = *N,N,N′,N′*-tetrakis(2-pyridylmethyl)-1,3-propanediamine and TPEN = *N,N,N′,N′*-tetrakis-(2-pyridylmethyl)-1,2-ethanediamine) have been investigated by Brinksma *et al.* in the epoxidation of alkenes[37] as well as oxidation of alcohols to their corresponding ketones or aldehydes.[38] An attractive feature of this type of ligand is that the route used in their synthesis allows for facile introduction of various groups either on the central diamine unit or by replacing one or more of the pyridyl rings. However, a key drawback with these catalysts in the oxidation of alkenes was that excess oxidant had to be used (8–16 equiv. of H_2O_2) to compensate for the extensive decomposition of H_2O_2 that occurred in the initial stage of the reaction. Furthermore, the solvent used, acetone, is potentially hazardous in the presence of H_2O_2.[39–41]

A remarkable observation was that, although the complex $[(Mn^{III,III}{}_2O(OAc)_2TPTN)]^{2+}$ catalysed the oxidation of a broad scope of alkenes including styrene, cyclohexene and *trans*-2-octene to the corresponding epoxides in good yields and turnovers (up to 870), its analogue $[(Mn^{III,III}{}_2O(OAc)_2TPEN)]^{2+}$, featuring a two-carbon spacer between the two *N*-donor sets in the ligand, was unreactive both in the epoxidation of alkenes and in the oxidation of alcohols.[38]

A lack of retention of configuration was reported, *i.e.* a mixture of *cis*- and *trans*-epoxide products were formed upon epoxidation of *cis*-β-methyl-styrene, and the observation of benzaldehyde in the oxidation of styrene and cinnamyl alcohol indicated[42] that radical intermediates are formed in the reaction mixture.

Although pre-prepared complexes were used in initial studies, *in situ* catalyst preparation was also investigated in the oxidation of alcohols.[38] Depending on the ligand used, a lag period of between 30 min and 3 h was observed. An (X-band) EPR spectroscopic and ESI-MS study of the reaction with *in situ* prepared catalysts was described.[38] Initially, the reaction mixture was EPR silent at 77 K; however, 15–90 min (depending on the ligand used) after addition of substrate and H_2O_2 a 16-line signal (A = 78 G), characteristic of a $Mn^{III,IV}{}_2$ complex was observed. ESI-MS measurements were less informative as only the mononuclear Mn^{II} complexes of the ligands were observed (*vide supra*).[22]

In 2008, Groni *et al.*[43] reported a combined EPR and UV/Vis absorption spectroscopic study of the species formed by reaction of the Mn^{II} complex of the ligand *N*-methyl-*N,N′,N′*-tris-(2-pyridylmethyl)-1,3-propanediamine in acetonitrile with excess H_2O_2. In addition to the observation of various manganese peroxy species and $Mn^{III,IV}{}_2$ dimers, they also isolated [Mn^{II}-(pyridine-2-carboxylate)$_2$(H_2O)$_2$] as the ultimate degradation

product of the complexes. Although the peroxy species observed would support the involvement of peroxy species in oxidation catalysis with complexes based on TPTN type ligands, in fact it was shown subsequently that the pyridine carboxylic acid formed can also provide substrate conversion.

Pijper *et al.*[33] studied the stability of ligands such as TPTN and their aminal precursors under the conditions employed in the earlier studies discussed above. Using a volatile substrate–product combination (2,3-dimethylbutene–2,2,3,3-tetramethyloxirane), which could be removed readily after the reaction, allowed for the ligand decomposition products to be identified by ^{1}H NMR spectroscopy. Under the reaction conditions employed, ligand decomposition to form pyridine-2-carboxylic acid (Fig. 5 and Scheme 7) was observed in all cases. Furthermore, it was demonstrated that, for example, replacement of the TPTN ligand by an equivalent amount of pyridine-2-carboxylic acid in the oxidation reactions resulted in identical activity and selectivity for a broad range of substrates.

The only notable differences were that with pyridine-2-carboxylic acid much less H_2O_2 (only 1.5 equiv.) was required to achieve the same levels of conversion and that the decomposition of H_2O_2 observed for the TPTN systems at the start of the reaction is absent when pyridine-2-carboxylic acid is used.[33] In conclusion, this latter study demonstrated a key challenge in oxidation chemistry in the possibility that the ligands employed are oxidised under reaction conditions. In general, it might be expected that ligand degradation would lead to loss of activity in a catalyst system. This particular example demonstrates clearly that this is not necessarily the case.

Although ligand degradation to pyridine-2-carboxylic acid is responsible for conversion observed under slightly basic conditions in the presence of ketones, this, *a priori*, does not mean that the use of polypyridyl amine as ligands for manganese is unpromising in oxidation catalysis when H_2O_2 is used as terminal oxidant.

On the contrary, following on from the excellent results reported by Stack and co-workers, using peracetic acid (PAA) as terminal oxidant,[44] Costas and co-workers demonstrated that this class of ligand can show exceptional efficiency (turn over frequency of 30 s^{-1}, 0.1 mol% catalyst, 1.1 equiv. H_2O_2 w.r.t. substrate) in the oxidation of alkenes with H_2O_2, when used in the presence of a moderate excess of acetic acid (14 equiv. w.r.t. substrate).[45] While $[Mn^{II}(OTf)_2(^{H,Me}PyTACN)]$, where ^{H,Me}PyTACN is 1,4-dimethyl-7-(pyridin-2′-yl)-methyl)-1,4,7-triazocylcononane, showed the best performance, the synthetically more accessible complex $[Mn^{II}(OTf)_2(BPMCN)]$, where BPMCN is *N*′,*N*′′-dimethyl-*N*′,*N*′′-bis(pyridin-2′′′-yl)methyl)cyclohexane-1,2-diamine, demonstrated conversions and yields of epoxides within acceptable ranges also (Fig. 6). The substrate scope was as broad as that obtained with PAA and a key advantage of the combination of acetic acid and H_2O_2, over the use of PAA, is in the oxidation of substrates, whose epoxide products are acid sensitive, such as 1-phenyl-cyclohex-1-ene and stilbene.

The $[Mn^{II}(OTf)_2(BPMCN)]$ system showed limited activity with respect to electron-poor and aromatic substrates. For the related complex $[Mn^{II}(OTf)_2(BPMEN)]$, where BPMEN is *N*′,*N*′′-dimethyl-*N*′,*N*′′-bis(pyridin-2′′-yl)methyl)ethane-1,2-diamine, a substantial decrease in conversion and yield was observed demonstrating the sensitivity of the activity observed to structural variation in these systems.

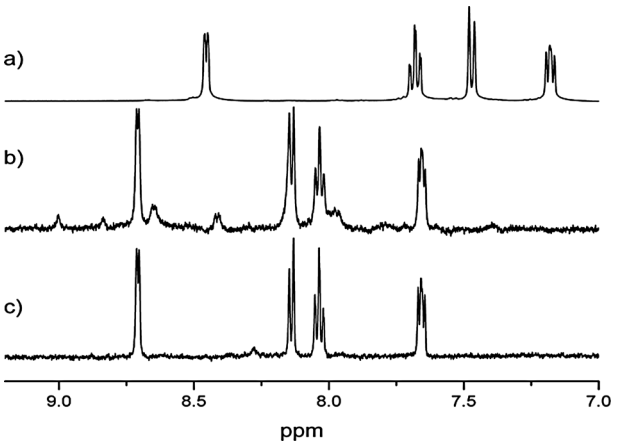
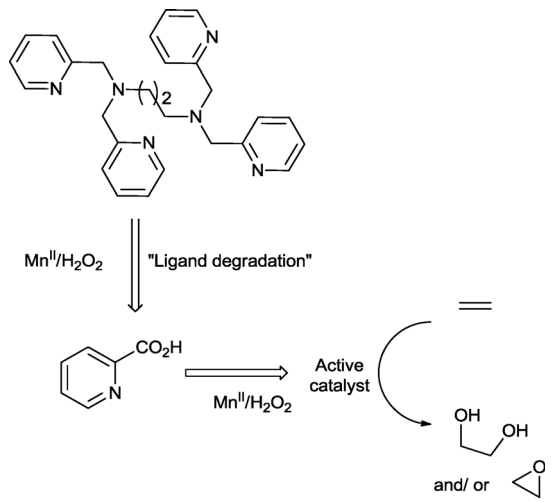


Fig. 5 ^{1}H NMR (400 MHz) spectra (only aromatic protons of the ligand are shown) of the reaction mixture with TPTN in acetone-d_6 (a) before and (b) 16 h after addition of H_2O_2 and (c) pyridine-2-carboxylic acid. Reproduced with permission from ref. 33. Copyright RSC 2010.



Scheme 7 Oxidative decomposition of TPTN ligand leads to a highly active oxidation catalyst based on pyridine-2-carboxylic acid.[33]

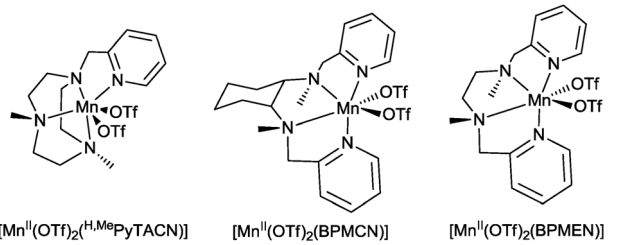


Fig. 6 Structures of Mn^{II} complexes discussed in the text.

A central question, however, is the role of acetic acid. Indeed given that PAA contains significant amounts of H_2O_2, it could be argued that the primary difference is that by using acetic acid and H_2O_2, traces of strong acids present in the PAA are avoided. It should be noted, however, that in the study of Pijper *et al.*[33] degradation of pyridyl amine based ligands was not observed under acidic conditions with H_2O_2, *i.e.* in the presence of acetic acid, and hence it could be speculated that one role played by the acetic acid is to inhibit ligand oxidation. Furthermore, it is apparent from the report of Costas and co-workers[45] and Dong *et al.*[34] (*vide supra*) that the *in situ* formation of PAA does not occur, as was noted earlier by Que and co-workers in the context of Fe^{II} catalysis.[46]

Several mechanistic differences between the acetic acid–H_2O_2 and the PAA systems demonstrate that the mechanisms involved in each case are likely to be different. The rate of oxidation of *trans*-stilbene is six times that of *cis*-stilbene in contrast to where PAA is used in which it is only twice the rate.[45] Furthermore, the difference in the Hammett sensitivity parameter between the acetic acid–H_2O_2 (ρ = –1.2) and PAA (ρ = –0.67) systems suggests that, although the mechanisms could be analogous, *i.e.* both active species are electrophilic, the active oxidant in each case is different. With regard to mechanistic considerations, epoxidation was found to be highly stereospecific, even for stilbene, indicating a concerted oxygen transfer to the alkene. These data, taken together with the incorporation of ^{18}O solely from H_2O_2, indicate a Lewis acid activation towards heterolysis of the O–O bond, which is assisted by the acetic acid. From a mechanistic perspective, however, the evidence available to date as to how these catalysts work is still limited.

Enantioselective epoxidation with pyridyl amine based manganese catalysts

The synthetic accessibility of complexes such as $[Mn^{II}(OTf)_2$-(BPMCN)] together with the remarkable activity with acetic acid–H_2O_2 demonstrated by Costas and co-workers[45] prompted Sun and co-workers[47,48] and later Costas and co-workers[49] and Lyakin *et al.*[50] to develop enantioselective epoxidation catalysts based on this class of ligand. In these series of reports the enantioselectivities achieved for a wide range of substrates are good to excellent, which holds considerable promise for the future.

Mechanistic considerations with pyridyl amine based manganese catalysts

On the basis of analogy with spectral data obtained for Fe^{II} complexes of the same ligands, Lyakin *et al.*[50] have proposed that the manganese systems involve a $[L(RCOO)Mn^{V}{=}O]$ species in alkene epoxidation. However, direct evidence of such manganese species is unavailable, except for the ^{18}O labelling studies reported by Costas and co-workers[45] that support a peroxy species as the oxygen transfer agent (*vide supra*). Indirect evidence, reported by Sun and co-workers,[48] can be found in the incorporation of ^{18}O from water to a minor degree in the epoxide products, which favours postulation of a Mn=O species as an intermediate.

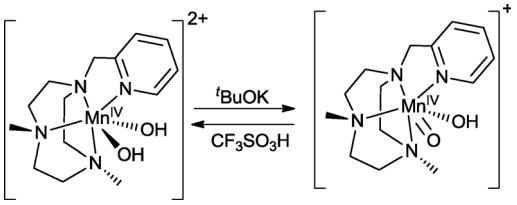


Fig. 7 Acid–base chemistry of $[Mn^{IV}(OH)_2(^{H,Me}PyTACN)]^{2+}$.[51]

The complex $[Mn^{II}(OTf)_2(^{H,Me}PyTACN)]$ warrants further discussion in regard to possible active intermediates in oxidation catalysis. As will be discussed below with Me_2EBC systems (Fig. 10), the ability to generate isolable high valent (Mn^{IV} and Mn^{V}) oxo and peroxo complexes presents the opportunity of testing the kinetic competence of such species. In the case of $[Mn^{II}(OTf)_2(^{H,Me}PyTACN)]$, Costas and co-workers have isolated the Mn^{IV} dihydroxy bound mononuclear complex $[Mn^{IV}(OH)_2(^{H,Me}PyTACN)]^{2+}$ by oxidation of $[Mn^{II}(OTf)_2$-$(^{H,Me}PyTACN)]$ with 10 equiv. of H_2O_2 at 0 °C.[51] The Mn^{IV} complex can be deprotonated reversibly to form a Mn^{IV} oxo species $[Mn^{IV}(=O)(OH)(^{H,Me}PyTACN)]^{+}$ (Fig. 7).

The Mn–O bands in the Raman spectrum (at 632 cm^{-1} for $[Mn^{IV}(OH)_2(^{H,Me}PyTACN)]^{2+}$ and 712 cm^{-1} for $[Mn^{IV}(O)(OH)$-$(^{H,Me}PyTACN)]^{+}$) underwent the expected isotopic shifts (−30 cm^{-1} based on the two atom oscillator approximation) in the presence of $H_2{}^{18}O$. The increased Raman shift of $[Mn^{IV}(O)(OH)(^{H,Me}PyTACN)]^{+}$ at 712 cm^{-1} is consistent with deprotonation to form a Mn=O bond. The complexes were characterised by ESI-MS and notably, despite the relatively high oxidation state, exchange of both the Mn–OH and Mn=O with $H_2{}^{18}O$ was observed. Although these species have demonstrated activity in C–H abstraction, it is important to note that they are wholly inactive in the epoxidation of alkenes, and hence cannot be viewed as 'active intermediates' in a catalytic cycle.[52] This point is discussed further below in regard to cyclam based systems.

In general, it can be expected that the range of ligands within the BPMEN class will expand in the near future to reach high enantio- and regio-selectivity routinely and to see application with more non-standard substrates such as the selective epoxidation of a precursor to epoxomicin, as demonstrated by Sun and co-workers[48] and the selective oxidation of the *cis*-alkene in the compound *trans,cis*-2,6-nonadienyl demonstrated by Costas an co-workers.[49] A key challenge however in light of the report of Pijper *et al.*[33] is that ligand oxidation can occur and the possible involvement of pyridine-2-carboxylic acid should not be neglected.

For this reason the recent report by Song *et al.*,[53] albeit not using H_2O_2, in which a more oxidatively stable pyridyl amide based ligand is designed is of note (Fig. 8). The system showed good activity in oxidation catalysis with *m*CPBA (*meta*-chloroperbenzoic acid) and PAA and mechanistic studies indicated that multiple pathways were involved, the relative importance of each depending on the exact conditions employed. In light of

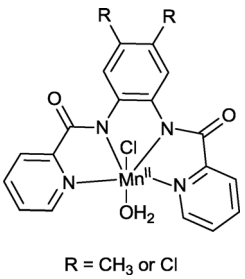


Fig. 8 Structure of amide based catalyst reported by Song *et al.*[53]

the systems described above it would be of interest for these systems to be studied with acetic acid–H_2O_2 also.

Trimethyl-triazacyclononane based ligands for manganese catalysed oxidations

Manganese complexes of the ligand *N,N′,N″*-trimethyl-1,4,7-triazacyclononane (TMTACN) were developed originally by Wieghardt and co-workers[54] as models for the oxygen evolving complex of photosystem II and to mimic dinuclear manganese catalases. These complexes have attracted the attention of several research groups towards oxidation catalysis over the last two decades.[55] This interest was prompted by the report by researchers at Unilever in 1994 that the complex $[Mn^{IV,IV}{}_2(\mu\text{-}O)_3(TMTACN)_2]^{2+}$ was a potent catalyst for low temperature stain bleaching with H_2O_2 and for epoxidation of alkenes, specifically 4-vinylbenzoic acid and styryl acetic acid in carbonate buffer (with 100 equiv. of H_2O_2 w.r.t. the substrate).[24,56]

Due to its application in laundry and dye bleaching, initial mechanistic studies focused on oxidations and speciation analysis in aqueous media. An important finding by Hage and co-workers with respect to later studies was the identification of carboxylic acid bridged dinuclear manganese complexes (*i.e.* $[Mn^{III,III}{}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(TMTACN)_2]^{2+}$) upon reduction of $[Mn^{IV,IV}{}_2(\mu\text{-}O)_3(TMTACN)_2](PF_6)_2$ in aqueous media.

With regard to potential active species, Lindsay-Smith and co-workers reported a UV/Vis absorption, EPR spectroscopic and ESI-MS study on the oxidation of cinnamates in buffered aqueous acetonitrile media.[57–60] They identified, by ESI-MS, mononuclear $Mn^{V}{=}O$ species[60] that could also be generated in oxidation reactions using a mononuclear Mn^{IV}-complex and from an *in situ* prepared Mn^{II}-complex using $MnSO_4$ and excess TMTACN ligand.[60] A central question, however, relates to the actual relevance of such species in the oxidation of alkenes, as discussed above and will be discussed in the last section.

Shortly after the initial reports of the activity of $[Mn^{IV,IV}{}_2(\mu\text{-}O)_3(TMTACN)_2]^{2+}$ by Hage and co-workers, efforts were directed to oxidation reactions in organic solvents. Although several manganese complexes based on TMTACN derivatives showed activity in organic solvents, a key challenge faced in applying Mn–TMTACN based catalysts was in overcoming wasteful disproportionation of H_2O_2.

A breakthrough came when De Vos and Bein demonstrated that, in acetone, only 2 equiv. of H_2O_2 were required to achieve good conversion (up to 80%) of alkenes to their corresponding epoxide products.[61] The dramatically increased efficiency in H_2O_2, achieved by carrying out reactions in acetone, could be assigned to the 'buffering' of the system by forming acetone–H_2O_2 adducts. However, the potential oxidation of acetone itself that competes with oxidation of organic substrates may be an alternate explanation for the effects observed. This is especially the case in light of the later discovery by De Vos *et al.* that efficient epoxidation of a range of alkenes could be achieved with suppression of decomposition of H_2O_2 (using 1.5 equiv. of H_2O_2) when carboxylic acids (*e.g.,* fumaric acid) and especially oxalate-buffered aqueous acetonitrile were used.[62]

It is interesting to note, in light of later studies (*vide infra*), that in the report of De Vos *et al.* acetic acid was not found to be effective in promoting the epoxidation activity of $[Mn^{IV,IV}{}_2(\mu\text{-}O)_3(TMTACN)_2]^{2+}$ whereas dicarboxylic acids and 1,3-diones were effective. Indeed, only 3 equiv. of acetic acid (w.r.t. catalyst) were employed. This, together with the generally poor enhancement seen with electron-rich carboxylic acids, would not be sufficient to form an active system. By contrast electron-poor dicarboxylic acids have an effective concentration of carboxylic acid groups twice that of their molar concentration and would be expected to form catalytically active bis-carboxylato bridged complexes. Lindsay-Smith, Schul'pin and co-workers demonstrated subsequently that with excess acetic acid (w.r.t. substrate) activity was observed in the oxidation alkanes and alkenes.[63]

Subsequent to the reports of De Vos and co-workers,[61,62] Berkessel and Sklorz reported that addition of L-ascorbic acid and sodium ascorbate was equally effective in suppressing H_2O_2 decomposition with this catalyst (prepared *in situ* from the ligand TMTACN and a Mn^{II} salt) and enabled both the epoxidation of alkenes and oxidation of alcohols with 2 equiv. of H_2O_2.[64]

Although the primary focus initially was on alkene epoxidation (Table 1), a key observation in terms of reactivity was made by De Vos and co-workers in the first example of a heterogenised version of the catalyst system.[65] In addition to obtaining the expected epoxide product upon oxidation of alkenes with H_2O_2, De Vos *et al.* observed the *cis*-dihydroxylation product also. Although low selectivity is not normally a positive result in catalysis, the observation of *cis*-dihydroxylation with a manganese catalyst and H_2O_2 was remarkable. Subsequent efforts to identify additives for the Mn–TMTACN system identified glyoxylic acid methylester methyl hemiacetal (GMHA) as an additive to promote the activity of the catalyst, suppress H_2O_2 disproportionation and provide moderate selectivity towards *cis*-dihydroxylation.[66]

A notable feature of the additive GMHA is that, although it suppressed H_2O_2 disproportionation completely, a significant lag period (1 h) was observed. Indeed a lag period is a common feature of the Mn–TMTACN system, except where L-ascorbic or oxalic acid is employed (*vide infra*). The lag phase indicates that the $[Mn^{IV,IV}{}_2(\mu\text{-}O)_3(TMTACN)_2]^{2+}$ complex must first undergo conversion to a catalytically active species. Indeed, Zondervan *et al.*[67]

Table 1 Comparison of efficiency in H_2O_2, conversion and selectivity for selected conditions covering a range of additives for the epoxidation of primary alkenes

Catalyst	Additive (mol%)	Equiv. of H_2O_2	Conv. (%)	T.O.N. Epoxide	T.O.N. *cis*-Diol	Ref.
1-Hexene						
Mn^{II}+TMTACN	Oxalic acid (0.2)/Na oxalate (0.2)	1.5	>99	666	0	62
1-Octene						
Mn–TMTACN	Oxalic acid (1)	1.3	86	724	0	71
Mn^{II}+TMTACN	L-Ascorbic acid (0.04)/Na L-ascorbate (0.16)	2.6	n.d.	1110	0	64
Mn–TMTACN	L-Ascorbic acid (1)	1.3	89	672	36	71
Mn–TMTACN	Salicylic acid (1)	1.3	75	590	30	71
Mn–TMTACN	Trichloroacetic acid (1)	1.3	66	200	115	71
Mn–TMTACN	2,6-Dichlobenzoic acid (1)	1.3	71	295	125	71

Mn–TMTACN = $[Mn^{IV,IV}{}_2(\mu\text{-O})_3(TMTACN)_2]^{2+}$.

noted earlier that a significant increase in the activity of $[Mn^{IV,IV}{}_2(\mu\text{-O})_3(TMTACN)_2]^{2+}$ in acetone was obtained when pretreated with excess H_2O_2 prior to addition of the substrate (in the case of benzyl alcohol oxidation).[67]

Subsequently, attention has focused on elucidating both the mechanism by which the catalysts work and understanding the specific role(s) played by various additives in enhancing the efficiency and selectivity of the reaction.[68] Initial studies focussing on catalytic properties had shown that addition of aldehydes (25 mol%) suppressed H_2O_2 decomposition and increased conversion. Furthermore, the selectivity between epoxide and (*cis*)-diol products was affected considerably by the nature of the aldehyde used. However, the origin of this effect became apparent during mechanistic studies in which it was realised that the corresponding carboxylic acids present as impurities were in fact responsible for the effects observed.[68] Reaction monitoring by UV/Vis absorption spectroscopy, together with comparison with data reported earlier by Wieghardt,[54] Hage,[21] and co-workers and independent synthesis of the complexes involved,[68] demonstrated that formation of bis-carboxylato bridged dinuclear manganese complexes, *i.e.* $[Mn^{III,III}{}_2(\mu\text{-O})(\mu\text{-RCO}_2)_2(TMTACN)_2]^{2+}$, was central to achieving reactivity (over 5000 turnovers) and selectivity (up to 7 : 1 *cis*-diol : epoxide product) with only 1.5 equiv. of H_2O_2 w.r.t. the substrate.[68]

In addition, de Boer *et al.*[69] highlighted that individual components in a reaction mixture can have more than a single role. In the case of the carboxylic acids the first role is to protonate $[Mn^{IV,IV}{}_2(\mu\text{-O})_3(TMTACN)_2]^{2+}$, thereby moving its reduction potential to more positive potentials. The change in reduction potential allows H_2O_2 to reduce[70] $[Mn^{IV,IV}{}_2(\mu\text{-O})_3(TMTACN)_2]^{2+}$ to first $Mn^{III,III}{}_2$ and then $^{II,II}{}_2$ redox states. The change in redox state enables rapid ligand exchange and ultimately the formation of the catalytically important $[Mn^{III,III}{}_2(\mu\text{-O})(\mu\text{-RCO}_2)_2(TMTACN)_2]^{2+}$ complex. This process is autocatalytic, *i.e.* a complex similar to $[Mn^{III,III}{}_2(\mu\text{-O})(\mu\text{-RCO}_2)_2(TMTACN)_2]^{2+}$ serves to catalyse the reduction of $[Mn^{IV,IV}{}_2(\mu\text{-O})_3(TMTACN)_2]^{2+}$. This sequence of events was shown to cause the lag-time observed, after which a sudden onset of the reaction occurred (Fig. 9).

The second role played by the carboxylic acid is to act as a bridging ligand and this allows for the (epoxide *vs.* *cis*-diol) selectivity and activity of the catalyst to be tuned. It should be noted that whereas electron withdrawing groups increase activity (presumably by facilitating the opening of the μ-oxo bridge of the complex and allowing for H_2O_2 to coordinate to one of the Mn^{III} ions), it is steric effects that dictate selectivity.[69] A third, but no less important role for the carboxylic acids, is to stabilise the $[Mn^{III,III}{}_2(\mu\text{-O})(\mu\text{-RCO}_2)_2(TMTACN)_2]^{2+}$ complex. In the absence of several equiv. of the carboxylic acid w.r.t. to the catalyst the activity is lost, concomitantly with the loss of $[Mn^{III,III}{}_2(\mu\text{-O})(\mu\text{-RCO}_2)_2(TMTACN)_2]^{2+}$. A final point is that at high carboxylic acid concentrations the selectivity shifts towards the epoxide product; the origin of this shift was found to be due to changes in solvent properties (specifically the 'wetness' of the solvent) and not to changes in the catalyst *per se*.

Mechanistic studies demonstrated the interdependence of solvent, initial catalyst oxidation state, water and carboxylic

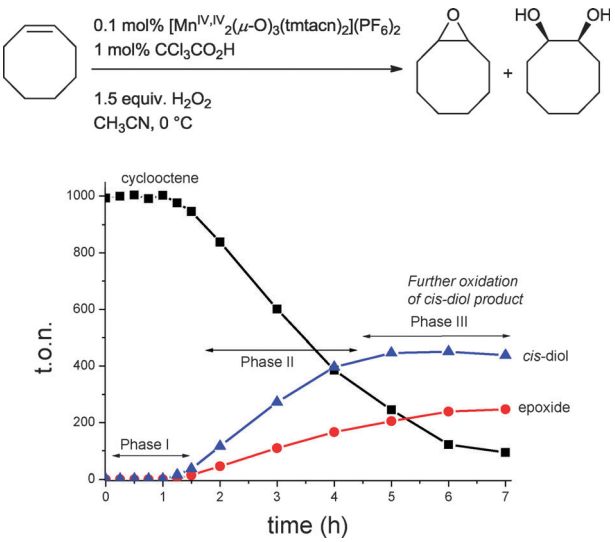


Fig. 9 Time dependence of consumption of cyclooctene and formation of its *cis*-diol and epoxide products catalysed by $[Mn^{IV,IV}{}_2(\mu\text{-O})_3(TMTACN)_2]^{2+}$. At the end of the lag phase (phase I), $[Mn^{IV,IV}{}_2(\mu\text{-O})_3(TMTACN)_2]^{2+}$ converts within several seconds to $[Mn^{III,III}{}_2(\mu\text{-O})(\mu\text{-RCO}_2)_2(TMTACN)_2]^{2+}$, determined by UV/Vis absorption spectroscopy, which is concomitant to the start of conversion of cyclooctene (phase II). Reproduced with permission from ref. 69. Copyright ACS (2007).

acid concentration, and the nature of the carboxylic acid employed in both the activity and the selectivity of the catalysis.[69] With regard to mechanism by which H_2O_2 is activated and the alkene oxidised, understanding the coordination chemistry of the $[Mn^{III,III}{}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(TMTACN)_2]^{2+}$ is essential.

$[Mn^{III,III}{}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(TMTACN)_2]^{2+}$ was shown to be stable in solution in the presence of substrate and, notably, in the presence of H_2O_2. Complexes of the type $[Mn^{III,III}{}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(TMTACN)_2]^{2+}$ show a wide range of redox and solvent dependent coordination chemistry, in particular with regard to the bridging μ-oxo moiety. Indeed, ESI-MS studies using $H_2{}^{18}O$ and CD_3CO_2H demonstrated that the μ-oxo bridge 'opens and closes' by reversible addition of water at a rate considerably faster than exchange of the carboxylato ligands.[69]

Evidence for redox changes or a change in their dinuclear structure throughout the catalytic cycle has not been found to date (Scheme 8). Absence of evidence, of course, does not preclude transient formation of a high-valent mononuclear species in the catalytic cycle, as proposed by several other groups.[55] However, it does imply that a mechanism in which the catalyst acts as a Lewis acid together with a proximal –O–H ligand should also be considered. Indeed the role of proximal hydrogen bond donors (*e.g.*, acetic acid) together with Lewis acidic metal centres in facilitating heterolytic cleavage of the O–O bond of H_2O_2 has been inferred in several systems (*vide infra*).

Although direct observation of the active species may not be possible, a key mechanistic tool in oxidation chemistry with H_2O_2 is atom tracking with ^{18}O labelling. de Boer *et al.*[69] found that only one of the oxygen atoms incorporated into the *cis*-diol product originates from H_2O_2 with the other oxygen atom being provided by H_2O, regardless of the type of carboxylic acid used as co-catalyst.

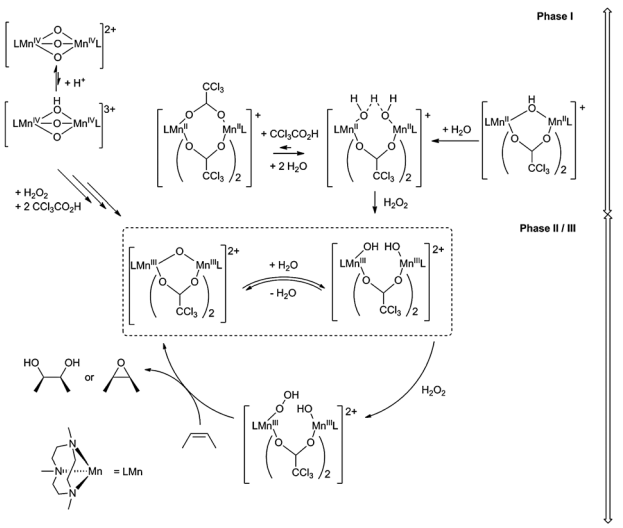
Concerning the origin of the oxygen atom in the epoxide product, the situation is less straightforward with both H_2O_2 and H_2O providing oxygen atoms, the extent of which depends on the particular carboxylic acid employed. A correlation between the selectivity of the catalyst/carboxylic acid system towards the *cis*-diol/epoxide ratio and the incorporation of oxygen into the epoxide from H_2O was observed. The incorporation into the epoxide product of oxygen from H_2O ranged from 18% for the 2,6-dichlorobenzoate complex (*cis*-diol/epoxide ratio 7) to 13.4% for the 2,4-dichlorobenzoic acid complex (*cis*-diol/epoxide ratio 2.7), to 3.4% for the salicylic acid (*cis*-diol/epoxide ratio 0.7).

It was concluded therefore that the more electrophilic the Mn–OH group of the proposed $Mn^{III}(OOH)$–$Mn^{III}(OH)$ active species, the higher the *cis*-diol:epoxide product ratio would be. It should be noted that with the more electron withdrawing CCl_3CO_2H, an unprecedented 33% incorporation of oxygen from H_2O into the epoxide product was observed.

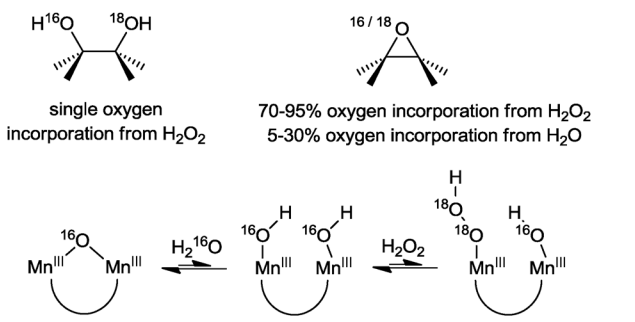
A final point worth noting with regard to mechanistic studies is that in the absence of carboxylic acid, when using the catalyst $[Mn^{III,III}{}_2(\mu\text{-}O)(\mu\text{-}CCl_3CO_2)_2(TMTACN)_2]^{2+}$, more oxygen from the H_2O_2 was incorporated into both the *cis*-diol and epoxide products, and a significant amount of *cis*-diol showed both oxygen atoms originating from H_2O_2. This observation can be rationalized by considering that the rate of exchange of Mn–O–Mn with H_2O is slower in the absence of an excess of carboxylic acid and, hence, after the first dihydroxylation with $H_2{}^{18}O_2$, $[Mn^{III,III}{}_2(\mu\text{-}{}^{18}O)(\mu\text{-}RCO_2)_2(TMTACN)_2]^{2+}$ would be regenerated and this would then form $[Mn^{III,III}{}_2({}^{18}O)({}^{18}O{}^{18}OH)(\mu\text{-}RCO_2)_2(TMTACN)_2]^{2+}$ (Scheme 9) in the next cycle. This highlights the importance of considering the rates of ligand exchange also when interpreting ^{18}O labelling data.

Overall, however, the data reported by de Boer *et al.*[68,69] supports a mechanism in which a dinuclear manganese complex acts both as a Lewis acid to activate the O–O bond of H_2O_2 towards heterolytic cleavage and to present a proximal Mn–O–H unit to facilitate epoxidation and to provide the 2nd oxygen in *cis*-dihydroxylation (Scheme 9). The increased reaction rates observed with more electron-poor carboxylic acids and the preference for electron-rich alkenes are manifestations of the electrophilic character of the active species also.

Although it may be tempting to expect that the mechanism by which the Mn–TMTACN catalysts operate is only 'tweaked'



Scheme 8 *cis*-Dihydroxylation and epoxidation of alkenes by $[Mn^{IV,IV}{}_2(\mu\text{-}O)_3(TMTACN)_2]^{2+}$.[69]



Scheme 9 Observed oxygen incorporation from H_2O_2 and H_2O in *cis*-diol and epoxide products for the oxidation of alkenes by $[Mn^{III,III}{}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(TMTACN)_2]^{2+}$ and possible H_2O_2 activated species.[69]

by variation in the additive used, *i.e.* complexes of the type $[Mn^{III,III}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(TMTACN)_2]^{2+}$ forming *in situ,* this is in fact not necessarily the case. Following on from the study of the effect of alkyl and aryl carboxylic acid additives, de Boer *et al.*[71] examined the systems of De Vos,[62] Berkessel[64] and co-workers, who first employed the use of additives with the Mn–TMTACN catalysts, *i.e.* reactions catalysed by $[Mn^{IV,IV}_2(\mu\text{-}O)_3(TMTACN)_2]^{2+}$ with oxalic acid or with L-ascorbic acid. The spectroscopy and catalysis observed with $[Mn^{IV,IV}_2(\mu\text{-}O)_3(TMTACN)_2]^{2+}$ in the presence of salicylic acid, L-ascorbic and oxalic acid were compared by de Boer *et al.*[71]

In the case of salicylic acid as additive, despite differences in the UV/Vis absorption spectroscopy during catalysis (compared with, *e.g.,* 3-hydroxybenzoic acid[69]) and the isolation of a green mononuclear complex [Mn^{III}(OH)(salicylate)(TMTACN)], in which the salicylic acid bound to the Mn^{III} ion *via* the carboxylate and the phenoxide, it was found that $[Mn^{III,III}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(TMTACN)_2]^{2+}$ species were nevertheless responsible for the catalysis observed. This example highlights the difficulties encountered in mechanistic studies in that the observation of a species does not necessarily imply its actual involvement in a catalytic cycle.

With L-ascorbic acid and oxalic acid, in contrast to the alkyl and aryl carboxylic acids, a lag period was not observed, *i.e.* conversion of the substrate began immediately upon addition of H_2O_2.[71] Mechanistically this difference can be understood in light of studies of the carboxylic acid promoted systems (*vide supra*, Scheme 8).[69] Both L-ascorbic acid and oxalic acid are reductants and hence the lag time, caused by the need for $Mn^{IV,IV}_2(\mu\text{-}O)_3(TMTACN)_2]^{2+}$ to be protonated and then reduced by H_2O_2 to occur, is absent.[69,72]

In the case of L-ascorbic acid as additive, the characteristic absorption spectrum of a $[Mn^{III,III}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(TMTACN)_2]^{2+}$ species was identified by UV/Vis spectroscopy.[73] This suggests that, except for the elimination of the lag time, mechanistically L-ascorbic acid promotes the reaction in a similar manner to the carboxylic acids. However, a caveat to such a conclusion is that electron-poor alkenes can be epoxidised with L-ascorbic acid as additive,[64] in contrast to the $[Mn^{III,III}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(TMTACN)_2]^{2+}$ catalysts, and hence in the former case a distinct mechanism may be in operation.

de Boer *et al.*[71] found that the oxalic acid/oxalate system developed by De Vos and co-workers,[62] presented considerable complexity with regard to mechanism. With the substrate, cyclooctene, initially only epoxidation was observed; however, at a certain point during the reaction the *cis*-dihydroxylation product was also formed. Addition of extra oxalic acid before the change in selectivity occurred (*ca.* 3 h) resulted in only epoxidation occurring over the entire reaction.[71] These observations can be understood by considering that oxalic acid is unstable and, for example, can undergo oxidation to CO_2. Hence the switch in reactivity observed is due to the eventual loss of the oxalic acid from the reaction mixture. Carboxylic acids present (formed by further oxidation of diols) are available to form the bis-carboxylato catalysts.

This latter mechanistic study highlights a general challenge in elucidating mechanisms in manganese oxidation catalysis; it is not necessarily the case that only a single mechanism can be in operation in a particular system. Although the mechanism switch observed with the oxalic acid–$[Mn^{IV,IV}_2(\mu\text{-}O)_3(TMTACN)_2]^{2+}$ system can be viewed as an extreme case, it is important to realise that changes in reaction conditions can switch mechanisms and that, as a reaction progresses, the changes in the reaction mixture (*e.g.*, solvent polarity and composition, water content, product inhibition) can be sufficient to trigger such switches.

Although the present discussion has focused on mechanistic aspects, in particular the role of additives in promoting the activity of the Mn–TMTACN family of complexes, a brief mention regarding enantioselective alkene oxidation is pertinent as well. A review of enantioselective epoxidation including systems catalysed by manganese is provided by Watkinson and co-workers and the interested reader is referred to it.[9] de Boer *et al.* demonstrated that enantioselective *cis*-dihydroxylation could be achieved with $[Mn^{IV,IV}_2(\mu\text{-}O)_3(TMTACN)_2]^{2+}$.[74] In earlier studies by Beller,[75] Bolm[76,77] and co-workers, chirality was introduced *via* chiral derivatives of the TMTACN ligand. In the report of de Boer *et al.* a different approach was taken that built on mechanistic studies carried out earlier. Those studies indicated that carboxylic acids acted as ligands in the catalytically active species. Hence screening of a wide range of chiral carboxylic acids identified *N*-acetylphenylglycine (*N*-Ac-D-Phg) in particular with 55% conversion and an ee of 54% in the *cis*-dihydroxylation of chromene (with 1.7 equiv. of H_2O_2, 0.4 mol% $[Mn^{III,III}_2(\mu\text{-}O)(\mu\text{-}N\text{-Ac-D-Phg})_2(TMTACN)_2]^{2+}$ and 4 mol% *N*-Ac-D-Phg at –20 °C in CH_3CN/H_2O 19 : 1).

The recognition that carboxylic acids act as ligands stimulated renewed interest in heterogeneous Mn–TMTACN catalysts first investigated by De Vos and co-workers.[78] In contrast to the early studies in which the complexes were immobilised on mesoporous silica gel *via* a specifically modified TMTACN derivative, Notestein and co-workers[79–81] reported that immobilisation of the catalyst by *in situ* reduction of $[Mn^{IV,IV}_2(\mu\text{-}O)_3(TMTACN)_2]^{2+}$ in the presence of carboxylic acid coated silica particles allowed for similar levels of activity to be observed, both for epoxidation and *cis*-dihydroxylation, as found previously in homogeneous reactions by de Boer *et al.* (*vide supra*).[69] Although characterisation of species formed in solution is relatively straightforward, when immobilised on surfaces/particles the application of spectroscopic methods becomes more challenging. Nevertheless, X-ray absorption spectroscopy and UV/Vis diffuse reflectance spectroscopy are particularly suited to studying the oxidation states of manganese and were applied in this case, demonstrating that $[Mn^{IV,IV}_2(\mu\text{-}O)_3(TMTACN)_2]^{2+}$ was grafted onto the silica surface as $[Mn^{III,III}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(TMTACN)_2]^{2+}$ (where R = carboxy functionalised silica surface), upon addition of H_2O_2.[81] As for the homogenous systems discussed above, in the case of the heterogenised catalyst, recycling was limited and tentatively ascribed to the effect of build-up of *cis*-diol in the reaction mixture.[81] Recently Bjorkman *et al.*[82] reported a microkinetic study of the heterogenised system with extensive use of modelling and concluded that the rate determining step was activation of

the complex with H_2O_2. While direct extension of the conclusions of their study to the homogeneous system cannot be made, it is nevertheless consistent with the observation that the resting state for the catalyst is the complex $[Mn^{III,III}{}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(TMTACN)_2]^{2+}$.[69]

Tetraazamacrocycles based ligands for manganese catalysed oxidations

Busch and co-workers have studied the tetraazamacrobicyclic ligand in depth over the last decade with regard to activity, substrate scope and mechanism. These complexes have shown activity in the epoxidation of alkenes employing H_2O_2[83–86] (and ^{t}BuOOH also) as terminal oxidant, as well as hydrogen abstraction.[87–91] In contrast to the TMTACN family of ligands the methyl groups on the non-bridging nitrogen atoms of the Me_2EBC ligand (where Me_2EBC is the cross-bridged ligand 4,11-dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane, Fig. 10) preclude formation of di- and multi-nuclear manganese complexes. Several manganese complexes of Me_2EBC have been characterised structurally, *i.e.* $[Mn^{II}(Me_2EBC)(Cl)_2]$,[83] $[Mn^{III}(Me_2EBC)(OMe)_2]^+$,[92] $[Mn^{III}(Me_2EBC)(OH)(OAc)]^+$ (ref. 92) and $[Mn^{IV}(Me_2EBC)(OH)_2]^{2+}$.[85]

The product distribution in the epoxidation of selected alkenes, catalysed by $[Mn^{II}(Me_2EBC)(Cl)_2]$ in acetone/water with excess H_2O_2 (17.7 equiv. w.r.t. substrate), together with ^{18}O-labelling studies and mass spectrometry provided considerable mechanistic insight into this system.[84] Of particular note, with regard to selectivity, is the oxidation of cyclohexene, which results in formation of cyclohexene oxide (18%) and cyclohexen-1-one (13%), as this indicates that the C–H abstraction ability (allylic oxidation) of the catalyst is substantial. However, the good selectivity in the oxidation of *cis*-stilbene and styrene to their epoxide products with minimal formation of benzaldehyde suggests that the catalyst does not generate radical species such as hydroxyl radicals.

Although catalysts based on this class of ligand have shown relatively modest activity (*i.e.* <45 turnovers in the oxidation of alkenes with excess H_2O_2 using the catalyst $[Mn^{II}(Me_2EBC)(Cl)_2]$),[84] these systems are highly amenable to mechanistic studies as a consequence of their stability in higher oxidation states, which facilitates their isolation. This allows for the kinetic competence of various species to be determined in stoichiometric reactions and hence, their involvement under catalytic conditions to be evaluated.

In aqueous solutions, $[Mn^{II}(Me_2EBC)(Cl)_2]$ undergoes facile aquation to form $[Mn^{II}(Me_2EBC)(OH)_2]$, which can be oxidised

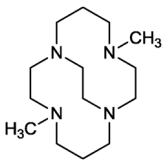
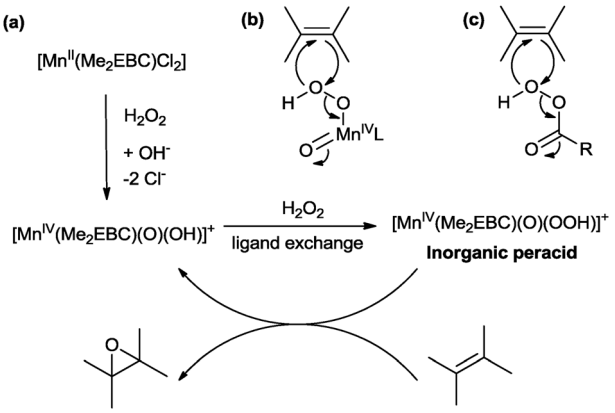


Fig. 10 Structure of Me_2EBC.



Scheme 10 (a) Proposed Lewis acid mechanism for epoxidation of alkenes using $Mn^{II}(Me_2EBC)Cl_2$ and H_2O_2. (b) Oxygen transfer by an inorganic peracid and (c) by an organic peracid.[84]

reversibly to both the Mn^{III} and Mn^{IV} oxidation states electrochemically. Indeed upon addition of H_2O_2 $[Mn^{II}(Me_2EBC)(OH)_2]$ is oxidised to $[Mn^{IV}(Me_2EBC)(OH)_2]^{2+}$, which when deprotonated forms a Mn=O species $[Mn^{IV}(Me_2EBC)(O)OH)]^+$. The isolated and structurally characterised complex $[Mn^{IV}(Me_2EBC)(OH)_2]^{2+}$ was tested as a stoichiometric oxidant in the oxidation of norbornylene, styrene and *cis*-stilbene. For all three substrates conversion was not observed even after standing for several days at room temperature. Generation of the Mn^{IV}=O analogue (by deprotonation of $[Mn^{IV}(Me_2EBC)(OH)_2]^{2+}$) did not result in alkene oxidation either, indicating that neither species is kinetically competent under reaction conditions with H_2O_2.[85]

This is supported further by ^{18}O labelling studies including the use of $^{18}O_2$, $H_2{}^{18}O$ and $H_2{}^{18}O_2$. Ready exchange of $[Mn^{IV}(Me_2EBC)(^{16}OH)_2]^{2+}$ with $H_2{}^{18}O$ to form $[Mn^{IV}(Me_2EBC)(^{18}O)(^{18}OH)]^+$ was observed, as noted later for related systems (*vide supra*).[85] Hence the absence of ^{18}O incorporation into the epoxide products confirmed the lack of involvement of $[Mn^{IV}(Me_2EBC)(OH)_2]^{2+}$. Overall ^{18}O labelling studies confirmed that for epoxidation the oxygen atom originates from H_2O_2. It should be noted, however, that, although these species do not engage in alkene epoxidation, $[Mn^{IV}(Me_2EBC)(OH)_2]^{2+}$ can engage in stoichiometric C–H abstraction.[88]

Busch and co-workers have proposed[84] a Lewis acid pathway rather than manganese oxo pathway; *i.e.* that $[Mn^{IV}(Me_2EBC)(O)(OH)]^+$ reacts with H_2O_2 to form $[Mn^{IV}(Me_2EBC)(O)(OOH)]^+$, which acts as an inorganic peracid and transfers an oxygen atom directly to alkenes similar to the mechanism by which organic peracids operate (Scheme 10). This hypothesis is supported by the detection of a signal assignable to $[Mn^{IV}(Me_2EBC)(O)(OOH)]^+$ by ESI-MS under catalytic conditions[85] and by recent DFT studies by Haras and Ziegler, which indicate that the mode of action of these complexes is *via* a Mn^{IV}–OOH species.[93]

Conclusions

In this review, several approaches to manganese based catalysts systems for the oxidation of alkenes with H_2O_2 are discussed.

At the simplest level 'ligand free' or, more correctly, *in situ* prepared catalysts offer considerable promise towards low cost catalyst systems not only for epoxidation of alkenes but also for *cis*-dihydroxylation. However, such systems do present drawbacks, especially with regard to substrate scope and the generally limited opportunities to tune selectivity and activity and in regard to enantioselective oxidations. The near stoichiometric efficiency with respect to terminal oxidant (H_2O_2), that has been achieved in several systems recently, means that such systems are now suitable for application even in large scale processes. From a mechanistic perspective it is apparent that, although such systems are simple to use, they are far from simple in regard to both the manganese itself and the roles played by other species in the reaction mixture.

With regard to enantioselective oxidation of alkenes the use of chiral ligands has shown some success. Indeed pyridyl amine based ligands offer perhaps the best prospects to date for epoxidation. By contrast, the synthetic challenges faced in preparing chiral Mn–TMTACN based catalysts have proven to be a serious impediment to progress in enantioselective oxidations. Here, the benefit of a mechanistic understanding is exemplified in the modest success achieved by use of chiral carboxylic acids as ligands.

From a mechanistic perspective, the ligand based systems discussed above indicate that whereas for C–H abstraction Mn=O species are likely to be involved, such species are less likely to be involved in alkene oxidations. Indeed, in contrast to porphyrin and salen based manganese catalysts, mechanistic data available for the systems discussed in this review generally point towards involvement of Lewis acid activation of H_2O_2 towards heterolytic cleavage of the O–O bond rather than a high valent manganese oxo species being responsible for oxygen transfer to alkenes.

Finally, perhaps the most important take-home message with regard to the mechanistic studies on these systems is that one should always remain open to the possibility that even in the simplest systems more than one mechanism may be in operation and that minor changes in conditions can lead to a switch between distinct mechanisms. This increases the difficulties encountered in mechanistic studies, of course, but on the positive side it also makes such studies much more fascinating.

Acknowledgements

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